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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,223	TYAGI ET AL.	
	Examiner	Art Unit	
	Angela M. Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *117-120 and 124-132* is/are pending in the application.

4a) Of the above claim(s) *130-132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *117-120 and 124-129* is/are rejected.

7)☒ Claim(s) *124,128 and 129* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Applicant's response filed on August 10, 2009 is acknowledged. Claims 117-120 and 124-132 are currently pending. In the response, Applicant amended claims 117, 118, 125, and 127-129. Claims 130-132 remain withdrawn from consideration as being drawn to a non-elected invention.

The following include new grounds of rejection. Any previously made rejections or objections not reiterated below have been withdrawn as being obviated by the amendment. Applicant's arguments filed on August 10, 2009 that remain pertinent to the new grounds of rejection have been fully considered, and they were persuasive, in part (see the "Response to Arguments" section). Since the rejection of claims 117-120 and 124-126 under 35 U.S.C. 103(a) as being unpatentable over Chakravorty in view of Jaber and further in view of Herrnstadt contains modifications that were not entirely necessitated by Applicant's amendment, this Office Action is made **NON-FINAL**.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see page 61). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

3. Claim 124 is objected to because of the following informalities: This claim appears to contain a typographical error in lines 3-4, where "polyoxyethylene phenyl ether X 100" is recited. Based on claim 117, it would appear that "polyoxyethylene phenyl ether" was intended.

Claims 128 and 129 are objected to because of the following informalities: These claims appear to contain a typographical error where "the same" is recited. It would appear that "the sample" was intended.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph (New Matter)

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 125, 128, and 129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Section 2163.03 of the MPEP states, "An amendment to the claims or the addition of a new claim must be supported by the description of the invention in the application as filed." *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989).

Section 2163.05 of the MPEP states, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement." *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

Claim 125 is drawn to the method of claim 117 and further requires that the mixing, homogenization, washing, and resuspension steps are conducted at neutral pH. The previous version of claim 125 stated that the method of claim 117 "in culture runs at neutral pH". Claims 128 and 129 are drawn to the method of claim 125 and recite that the method further comprises PCR amplification using specific primer pairs. Applicant does not identify the portions of the original disclosure that provide support for the amendment to claim 125.

The original disclosure has been carefully reviewed, but it does not appear to provide support for the limitations recited in amended claim 125. In particular, the original disclosure does not appear to provide proper support for conducting the mixing, homogenization, washing, and resuspension steps at neutral pH as required by amended claim 125, and also claims 128-129, which depend from claim 125. The specification describes the method of claim 117 (see pages 10-12, for example), but it does not describe the pH at which each step of the method (*i.e.* mixing, homogenizing, washing, and resuspension) was conducted. Since the USP solution is not a neutral pH solution, but rather, a slightly alkaline solution with a pH between 7.3 and 7.7, and since the resuspension solutions are not inherently neutral pH solutions, it is not inherent that the mixing, homogenizing, washing, and resuspension steps of the method recited in claim 117 and described at pages 10-12 of the specification are performed at neutral pH as required by claims 125, 128, and 129. It is also noted that the amendment to claim 125 does not constitute mere rephrasing of the original language "wherein the method in culture runs as neutral pH". As

discussed previously, this language is entirely ambiguous, and the original disclosure does not provide any additional clarification as to the intended meaning. Since the amendment to claim 125 does not appear to find adequate support in the original disclosure, claims 125, 128, and 129 have been rejected under 35 U.S.C. 112, first paragraph for incorporating new matter.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 117-120 and 124-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Herrnstadt et al. (US 6,027,883; cited previously).

These claims are drawn to a method for processing clinical samples using a composition comprising three solutions.

Regarding claim 117, Chakravorty teaches a method comprising:

(a) obtaining a clinical sample (page 114, section 2.1),

(b) mixing 1.5 – 2 volumes of a first solution with the sample and homogenizing the sample (see page 114, section 2.2.1, where the IRS solution of Chakravorty comprises: 5 M GITC, 50 mM Tris-Cl, pH 7.5, 25 mM EDTA, 0.5% Sarcosyl, and 0.2 M β-mercaptoethanol),

(c) centrifuging the homogenate to form a pellet (page 114, section 2.2.1),

(d) washing the pellet obtained in step (c) with the first solution (page 114, section 2.2.2),

(e) washing the pellet of step (d) with water (page 114, section 2.2.2), and

(f) resuspending the water-washed pellet in solution A (*i.e.* a 10% suspension of a chelating resin), solution B (*i.e.* a 0.03% polyoxyethylene phenyl ether solution), and solution C (*i.e.* a 0.3% solution of polysorbate 20) (page 114, section 2.2.3).

Chakravorty further teaches that the supernatant obtained after step (e) is subjected to PCR amplification to amplify mycobacterial DNA (page 114).

Regarding claim 118, Chakravorty teaches homogenization for 30-60 seconds (page 114, column 1). This range of homogenization times lies within the claimed range of 20-120 seconds.

Regarding claim 119, Chakravorty teaches that the above process can be performed in approximately three hours (page 116, column 2).

Regarding claim 120, the 5 M concentration of GITC is about 4 M, about 5 M, and about 6 M, and the 0.2 M concentration of β-mercaptoethanol is about 0.1 M or about 0.2 M. This concentration of β-mercaptoethanol is also within the claimed range of 0.1-0.2 M. It is further

noted that the intended use recitations "for processing samples for culture and smear", "for processing of samples for culture, smear, and PCR", and "samples processed for smear and PCR" have not been accorded patentable weight since they are intended use recitations that do not further limit the structural features of the positively recited method steps (MPEP 2111.02 II).

Regarding claim 124, Chakravorty teaches obtaining PCR-amplifiable DNA by adding 0.03% polyoxyethylene phenyl ether solution and heating the sample at 90°C for 40 minutes (page 115, column 1). This surfactant concentration lies within the claimed range of 0.01 - 0.1%. It is also noted that the method of Chakravorty is inherently capable of producing PCR-amplifiable RNA in addition to PCR-amplifiable DNA.

Regarding claim 125, the method of Chakravorty is performed at pH 7.5 (page 114) rather than at neutral pH.

Regarding claim 126, Chakravorty does not specify that the samples were stored at about -20°C for a time up to two months. However, it is inherent that the samples can be processed for PCR, smear microscopy, and culture.

Chakravorty teaches the use of 5 M GITC in the first solution rather than 4-6 M GuHCl as required by claim 117. Also, Chakravorty does not teach adding sterile water to the homogenate as required by claim 117. Furthermore, Chakravorty also teaches that the above sample processing method can be performed in approximately three hours (page 116, column 2) rather than the 1-2 hours required by claim 119. Finally, regarding claim 125, Chakravorty teaches performing the method at the slightly alkaline pH of 7.5 rather than at neutral pH.

Jaber teaches a method for isolating DNA from *Mycobacterium tuberculosis* (pages 578-579). The method of Jaber comprises the following steps: (1) cell lysis in 6 M GuHCl, 50 mM

EDTA, 1 mM 2-mercaptoethanol, 0.05% Tween 80; (2) ethanol precipitation, (3) washing with lysis buffer, (4) phenol-chloroform and chloroform-isoamyl alcohol extraction, and (5) ethanol precipitation (see page 579).

Regarding claim 117, Jaber teaches that the chaotropic agent guanidinium hydrochloride, (GuHCl), "inactivates DNase and RNase, dissociates nucleoprotein, and disturbs cellular and subcellular structure, and its pH and ionic strength favor the native form of DNA (page 579, column 2)."

Herrnstadt teaches methods of isolating nucleic acids (see abstract and column 1, lines 50-61). Regarding claims 117-120 and 124-126, Herrnstadt teaches that guanidine hydrochloride and guanidine isothiocyanate are chaotropic agents suitable for disrupting tissue samples for subsequent DNA or RNA isolation (column 1, lines 35-40).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute GuHCl for GITC in the sample processing method taught by Chakravorty. An ordinary artisan would have been motivated to do so, because as evidenced by the teachings of Jaber (see pages 579-580) and Herrnstadt (see column 1, lines 35-40), GuHCl and GITC were known in the art at the time of invention to be equivalents useful for the same purpose, namely cell lysis. As noted in MPEP 2144.06, the substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, no evidence has been presented to suggest that the use of GuHCl is associated with unexpected results. Regarding step (d) in the method of claim 117, it also would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to dilute the homogenate prepared in the method resulting from the combined teachings of Chakravorty and

Jaber using sterile water. An ordinary artisan would have been recognized that doing so would improve the method by decreasing the viscosity of the homogenate, and thereby, improving the centrifugation step. An ordinary artisan also would have recognized that the use of sterile water for the dilution step would have reduced the likelihood of contamination stemming from the presence of microorganisms in the water. It is also noted that dilution of the homogenate via the addition of sterile water constitutes an alteration of the concentration of the components of solution 1 used to prepare the homogenate. As noted in MPEP 2144.05, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." In this case, no evidence has been presented to suggest that the claimed concentrations (*i.e.* those concentrations resulting from dilution of the homogenate with sterile water) are critical, and therefore, the claimed dilution step is *prima facie* obvious in view of the combined teachings of the cited references in the absence of secondary considerations.

Finally, regarding claims 118, 119, 125, and 126, an ordinary artisan would have been motivated to optimize the homogenization time, the total processing time, sample storage conditions, and the pH at which the method was conducted in order to achieve the desired results. Regarding the claimed range of homogenization times, attention is directed to MPEP 2144.05 I, which states that "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). In this case, the range of 30-60 seconds disclosed by Chakravorty lies within the claimed range of 20-120 seconds, and therefore, a *prima facie* case of obviousness exists. An ordinary artisan also would

have been motivated to minimize the time required for performance of the method in order to increase efficiency and to optimize the pH at which the steps in the method were conducted in order to obtain the desired results (*e.g.*, optimal homogenization and resuspension). An ordinary artisan also would have been motivated to store the samples in the manner required by claim 126 (*i.e.* at about -20C for a time up to two months), since these sample storage conditions were conventional in the art at the time of the invention. Moreover, as noted in MPEP 2144.05, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Routine optimization is not inventive, and no evidence has been presented to suggest that the selection of the claimed homogenization times, processing times, sample storage conditions, or pH values was other than routine or that the results should be considered to be unexpected compared to the prior art. Thus, the methods of claims 117-120 and 124-126 are *prima facie* obvious in view of the combined teachings of the cited references.

7. Claims 127-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chakravorty et al. (FEMS Microbiology Letters (2001) 205: 113-117; cited previously) in view of Jaber et al. (Tubercle and Lung Disease (1995) 76: 578-581; cited previously) and further in view of Herrnstadt et al. (US 6,027,883; cited previously) and further in view of GenBank Accession No. U22037 (March 1999; cited previously) and further in view of Marchetti et al. (Journal of Clinical Microbiology (1998) 36(6): 1512-1517; cited previously) and further in view of Buck et al. BioTechniques (1999) 27(3): 528-536; cited previously).

The combined teachings of Chakravorty, Jaber, and Herrnstadt render obvious the methods of claims 117-120 and 124-126, as discussed above.

Regarding claims 127-129, Chakravorty teaches using a set of primers designed from the *Mycobacterium tuberculosis* devR gene to amplify DNA isolated using the above method (page 114, column 2). However, Chakravorty does not teach amplification using two sets of primers, wherein each primer set targets the devR gene and produces amplification products of 308 bp and 164 bp as required by claims 127-129.

GenBank Accession No. U22037 teaches the complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene. The primers taught by Chakravorty are contained in this sequence and produce a 513 bp amplification product.

Marchetti teaches methods for amplifying *Mycobacterium tuberculosis* DNA by PCR (see abstract and page 1513). Marchetti compared the sensitivity of four different PCR primer pairs and determined that the use of primers designed to amplify shorter targets resulted in more sensitive detection than primers designed to amplify longer targets (see abstract and pages 1514-1515). Marchetti further stated, "PCR3 and PCR4, whose final amplification products are 106 and 123 bp long, respectively, showed the best results in terms of sensitivity compared to those of PCR1 and PCR2, which amplify longer fragments (223 and 143 bp, respectively). This suggests the need to choose the correct primers, with those amplifying relatively shorter DNA sequences, which are thus less prone to fragmentation, being favored (page 1515, column 2)."

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck

also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize any set of primer pairs designed from the known *Mycobacterium tuberculosis* devR gene to amplify DNA isolated by the method resulting from the combined teachings of Chakravorty, Jaber, and Herrnstadt. Since Marchetti taught that the use of primers designed to amplify short targets in the *Mycobacterium tuberculosis* genome resulted in increased sensitivity (pages 1514-1515), an ordinary artisan would have been motivated to design primer pairs targeting sequences shorter than the 513 bp region targeted by Chakravorty. An ordinary artisan would have had a reasonable expectation of success designing these primers since the complete devR gene sequence was known in the art at the time of invention as evidenced by GenBank

Accession No. U22037. An ordinary artisan also would have had a reasonable expectation of success in using the primers in the method resulting from the combined teachings of Chakravorty, Jaber, and Herrnstadt, since Buck demonstrated that essentially all primers were capable of an equivalent degree of extension when hybridized to a complementary target. Therefore, absent any secondary considerations, the claimed methods are *prima facie* obvious in view of the combined teachings of Chakravorty, Jaber, Herrnstadt, Marchetti, GenBank Accession No. U22037, and Buck.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty, Jaber, and Herrnstadt. The complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene, which is disclosed in GenBank Accession Number U22037, presented the ordinary artisan with a finite number of possible primers for amplification. Then, since Buck taught that a large number of primers designed to detect the same target functioned reasonably well, an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by applying the teachings

of Marchetti to the devR gene targeted by Chakravorty. Thus, the methods of claims 127-129 are *prima facie* obvious over the cited references in the absence of secondary considerations.

Response to Arguments

8. The previously made objections to claims 117, 118, and 127-129 and the rejections of claims 117-120 and 124-129 made under 35 U.S.C. 112, second paragraph have been withdrawn in view of the amendment. Accordingly, Applicant's arguments filed on August 10, 2009 regarding these objections and rejections have been considered, but they are moot as the rejections and objections have been withdrawn.

Applicant's arguments filed on August 10, 2009 remain pertinent to the rejections of claims 117-120 and 124-129 made previously under 35 U.S.C. 103(a). These arguments have been fully considered, and they were persuasive, in part.

Regarding the rejection of claims 117-120 and 124-126 under 35 U.S.C. 103(a) as being unpatentable over Chakravorty in view of Jaber and further in view of Herrnstadt, Applicant first argues that Chakravorty does not teach adding sterile water to a homogenate as required by claim 117. Applicant argues that, at best, Chakravorty teaches adding water and the disclosed inhibitor removal (IRS) solution to a sample at the same time and homogenizing the resulting mixture (see pages 8-9 and also pages 10-11).

This argument with respect to the teachings of Chakravorty as they relate to step (d) in the method of claim 117 was persuasive, and the rejection of claims 117-120 and 124-126 under 35 U.S.C. 103(a) as being anticipated by Chakravorty has been modified accordingly. As discussed above in the modified rejection, although Chakravorty does not teach adding sterile

water to the homogenate as required by claim 117, it would have been obvious for the ordinary artisan to dilute the homogenate by adding sterile water prior to the centrifugation step. An ordinary artisan would have been motivated to do so, in order to obtain a less viscous mixture, and therefore, facilitate the centrifugation process. It is also noted that adding sterile water to the homogenate as required by claim 117 results in an alteration in the concentration of the components of solution 1 in the homogenate, which is *prima facie* obvious in the absence of unexpected results (MPEP 2144.05).

Applicant also argues that the ordinary artisan would have neither a motivation nor a reasonable expectation of success in substituting the GuHCl taught by Jaber for the GITC taught by Chakravorty, since Jaber teaches using GuHCl to lyse mycobacteria, which are very different from the tissue samples disrupted by the GITC in the method of Chakravorty (see pages 9 and 11-13). Applicant argues that the differences between the samples used in the methods of Chakravorty and Jaber would not have led the ordinary artisan to consider GuHCl and GITC to be art-recognized equivalents useful for the same purpose as stated in the rejection (page 12). Applicant also argues that the lysis buffers used by the two references have more differences than the chaotropic agent, and therefore, the ordinary artisan would not have had a reasonable expectation of success in substituting one chaotropic agent for another (page 11). Applicant also argues that the rejection provides no explanation of why the ordinary artisan would be motivated to substitute GuHCl for GITC in the lysis buffer of Chakravorty and no discussion of why the ordinary artisan would have expected the substitution to work (page 11). Finally, Applicant argues that the cited passage of Jaber does not indicate that GuHCl will be useful for complete

protein denaturation and isolation DNA from tissue, since additional denaturants are used in the disclosed method (page 12).

These arguments were not persuasive, because the rejection contains a clear explanation of why one of ordinary skill in the art at the time of invention would have been motivated to substitute GuHCl for GITC in the method of Chakravorty. As discussed above, the prior art of Jaber and Herrnstadt establishes that GuHCl and GITC are art-recognized equivalents known to be useful for the same purpose, and therefore, the ordinary artisan would have been motivated to substitute one for the other with a reasonable expectation of success. Furthermore, it is noted that only a reasonable expectation of success is required to establish a *prima facie* case of obviousness (MPEP 2143.02 I). In this case, since the cited references teach that the GuHCl and GITC are useful for disrupting tissue or bacterial cells, the ordinary artisan would have had a reasonable expectation of success in substituting the less toxic GuHCl of Jaber for the more toxic GITC of Chakravorty. Also, by providing evidence that ordinary artisans considered GuHCl and GITC to be equivalents useful for disrupting bacterial cells and tissues, the rejection also indicates why the ordinary artisan would have expected the substitution to work.

It is also noted that the lysis buffers of Jaber and Chakravorty are not as different as Applicant argues. The buffer of Jaber contains 6 M GuHCl, 50 mM EDTA, 1 mM 2-mercaptoethanol, and 0.05% Tween (page 579, column 2), whereas the buffer of Chakravorty contains 5 M GITC, 50 mM Tris-Cl, 25 mM EDTA, 0.5% Sarcosyl, and 0.2 mM 2-mercaptoethanol at pH 7.5 (page 114, section 2.2.1). Each of these two buffers contains the same basic elements, namely a cell-disrupting guanidine-based chaotropic agent, a chelating agent, a reducing agent, and a detergent at similar concentrations, and also functions to lyse cells

based on the same principle (*i.e.* the use of a chaotropic agent). Accordingly, upon reading the Herrnstadt reference, which teaches that GuHCl and GITC are each useful for disrupting tissue samples, together with the Jaber and Chakravorty references, the ordinary artisan would have been motivated to substitute GuHCl for GITC in the method of Chakravorty with a reasonable expectation of success.

Applicant further argues that the cited references teach the use of GITC and GuHCl as cell lysis agents, whereas the claimed invention uses GuHCl to preserve mycobacteria present in the clinical sample while destroying the remaining components of the sample (page 12). Applicant argues that in the absence of a teaching in the prior art that GuHCl can be used to preserve mycobacteria present in a clinical sample while destroying the remaining components of the sample, there is no motivation to substitute GuHCl for GITC (pages 12-14).

This argument was not persuasive, because the claims do not currently require GuHCl to preserve mycobacteria present in the clinical sample while destroying the remaining components of the sample. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is also noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In this case, as discussed above, the ordinary artisan would have been motivated to substitute one chaotropic agent for another when practicing the method of Chakravorty since the GITC used in the method of Chakravorty and the GuHCl used in the method of Jaber were each known in the art to be useful chaotropic

agents for disrupting cells and tissues. Attention is also directed to MPEP 2144, which states, "The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." See, *e.g.*, *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991).

Applicant further argues that there is no motivation to combine the teachings of the cited references, since the method of Chakravorty utilizes centrifugation to isolate the DNA sample, whereas the method of Jaber utilizes precipitation to isolate DNA (pages 13-14). Applicant argues that the ethanol precipitation step is taught by Jaber to be critical, and therefore, an ordinary artisan would not reasonably expect a method wherein centrifugation is substituted by precipitation to produce PCR amplifiable DNA as required by the claimed methods (pages 13-14). Applicant further argues that these differences in the procedures of Chakravorty and Jaber do not suggest substituting GITC with GuHCl as stated in the rejection (pages 13-14).

This argument was not persuasive, because as discussed above, an ordinary artisan would have been motivated to substitute known art-recognized equivalents, such as GuHCl and GITC, when preparing the buffers used in the method of Chakravorty. As discussed above, the

substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results (MPEP 2144.06). Also, since both the centrifugation-based method of Chakravorty and the precipitation-based method of Jaber utilized a guanidine-based chaotropic agent to obtain the homogenate, the ordinary artisan would have expected that the substitution of one guanidine-based chaotropic agent for another would give similar if not identical results. In other words, the ordinary artisan would not have considered the fact that the method of Jaber comprises precipitation rather than centrifugation to imply that the GuHCl used to obtain the cell lysate was unsuitable for use in a method comprising the use of GITC to obtain a homogenate followed by centrifugation, particularly since the teachings of Jaber regarding the precipitation step in no way imply that the use of guanidine hydrochloride is limited to precipitation based methods. Again, it is noted that only a reasonable expectation of success is required to establish a *prima facie* case of obviousness (MPEP 2143.02). Since, as evidenced by Jaber and Herrnstadt, GITC and GuHCl were known in the art to be useful chaotropic agents for lysing bacterial cells or cells present in a tissue sample, the ordinary artisan would have expected to obtain DNA suitable for PCR amplification upon substitution of one guanidine-based chaotropic agent for another. It is also noted that no evidence other than attorney arguments has been provided to suggest that the substitution of GuHCl for GITC in the method of Chakravorty would not produce PCR amplifiable DNA or that GuHCl would not function in the same manner as the GITC taught by Chakravorty. As noted in MPEP 2145, attorney arguments cannot substitute for evidence when evidence is necessary.

Applicant further argues that the rejection does not explain why the ordinary artisan would not simply substitute the lysis buffer of Jaber for the lysis buffer of Chakravorty instead of

substituting GITC for GuHCl (pages 14-15). Applicant argues that the buffers of Jaber and Chakravorty are different, and there is no reason to substitute elements of one buffer for those of the other (pages 14-15). Applicant also argues that the teachings of the cited references must be considered as a whole, and that neither Jaber nor Chakravorty teaches that any of the components can be substituted with other components or altered (pages 14-15). Based on the differences between the two buffers and the absence of an explicit suggestion of substitution of buffer components, Applicant argues that a *prima facie* case of obviousness has not been established (pages 14-15). Applicant also notes that the methods of Jaber require phenol-chloroform extraction and ethanol precipitation, and that these steps are not part of the methods conducted by Chakravorty.

These arguments have been fully considered, but they were not persuasive. As an initial matter, it is noted that the requirements for establishing a *prima facie* case of obviousness include consideration of what would have been suggested to the ordinary artisan based on the combined teachings of the cited references as a whole, but there is no requirement for the examiner to assess and analyze every possible method that could be considered to result from the combined teachings of the cited references as Applicant's arguments suggest (MPEP 2142). In this case, as discussed above, the teachings of the cited references suggest that any guanidine-based chaotropic agent could be used to practice the method of Chakravorty. Also, as discussed above, the buffers of Chakravorty and Jaber are not as different as Applicant argues, since they each contain the same basic elements: a guanidine-based chaotropic agent, a chelating agent, and a nonionic detergent, and a reducing agent. As a result, the ordinary artisan would have expected substitution of one guanidine-based chaotropic agent for another to meet with predictable results.

Furthermore, as noted in MPEP 2144.06, "An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious." *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, as noted in MPEP 2145, "A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in *KSR* identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper 'functional approach' to the determination of obviousness as laid down in *Graham*." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395-97. Finally, Applicant's arguments regarding the phenol-chloroform extraction and ethanol precipitation steps in the method of Jaber were unpersuasive, because, since the methods of Chakravorty and Jaber each utilized a guanidine-based chaotropic agent to obtain a homogenate, the ordinary artisan would have expected that the substitution of one guanidine-based chaotropic agent for another would give similar if not identical results. In other words, the ordinary artisan would not have considered the fact that the method of Jaber comprises organic extraction and ethanol precipitation to imply that the GuHCl used to obtain the cell lysate was unsuitable for use in a method comprising the use of GITC to obtain a homogenate followed by different nucleic acid purification steps, particularly since the teachings of Jaber regarding these steps in no way implies that the use of guanidine hydrochloride is limited to the disclosed methods. Again, it is noted that only a reasonable expectation of success is required to establish a *prima facie* case of obviousness (MPEP 2143.02). It is also noted that no evidence other than attorney arguments has been provided to suggest that the substitution of GuHCl for GITC in the method of Chakravorty would not produce PCR amplifiable DNA or that GuHCl would not function in the same manner as the

GITC taught by Chakravorty. As noted in MPEP 2145, attorney arguments cannot substitute for evidence when evidence is necessary.

Finally, Applicant's attention is directed to MPEP 2143, which discusses the findings of fact that must be made to support a conclusion of obviousness based on the rationale that it is obvious to substitute one known element for another to obtain predictable results in the absence of secondary considerations. This section of the MPEP states that the following must be articulated: (1) a finding that the prior art contained a device (method, product, etc.) which differed from the claimed device by the substitution of some components (step, element, etc.) with other components (**In this case, the method of Chakravorty discloses the claimed USP solution with the exception that GITC is disclosed instead of GuHCl**); (2) a finding that the substituted components and their functions were known in the art (**In this case, Jaber and Herrnstadt teach that GuHCl and GITC are chaotropic agents useful for disrupting cells and tissues**); and (3) a finding that one of ordinary skill in the art could have substituted one known element for another, and the results of the substitution would have been predictable (**In this case, both compounds were readily available and of similar chemical structure. Accordingly, the ordinary artisan would have been able to substitute one chaotropic agent for the other with the expectation of predictable results**). Thus, the conclusion the methods of claims 117-120 and 124-126 are obvious in view of the teachings of Chakravorty, Jaber, and Herrnstadt has been adequately supported.

Since Applicant's arguments were not persuasive, the rejection of claims 117-120 and 124-126 under 35 U.S.C. 103(a) as being unpatentable over Chakravorty in view of Jaber and further in view of Herrnstadt has been maintained with modifications.

Regarding the rejection of claims 127-129 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Chakravorty, Jaber, Herrnstadt, GenBank Accession No. U22037, Marchetti, and Buck, Applicant first argues that these claims depend from claim 117, which is not rendered obvious by the combined teachings of the primary combination of references (*i.e.* Chakravorty, Herrnstadt, and Jaber), and that the additional secondary references cited in the rejection do not overcome the deficiencies present in the primary combination of references (see page 15). This argument was not persuasive, because as discussed above, the combined teachings of Chakraborty, Jaber, and Herrnstadt render obvious the methods of claims 117-120 and 124-126.

Applicant also argues that there is no motivation to combine the cited references and select the claimed primers from the large number of primers suggested by the prior art (see pages 15-16). Applicant further argues that the rejection does not establish why the ordinary artisan would have considered the claimed primers to be useful (see page 15).

These arguments were not persuasive, because as discussed previously, an ordinary artisan would have been motivated to apply the teachings of Marchetti regarding the dependence of PCR sensitivity on target length to the method resulting from the combined teachings of Chakravorty, Jaber, and Herrnstadt. Application of the teachings of Marchetti to the method resulting from the combined teachings of Chakravorty, Jaber, and Herrnstadt would result in the design of primer pairs (*e.g.* the claimed primer pairs) that produce shorter amplified products and a method with improved sensitivity. When designing primers that produce shorter amplified products as suggested by Marchetti, the ordinary artisan would have been motivated to design and synthesize any primer from the known *M. tuberculosis* devR gene, such as the claimed

primers, recognizing their suitability for the intended purpose. Since, as evidenced by Buck, essentially any primer could be reasonably expected to function in an amplification method, the ordinary artisan would have expected that virtually any primer pair designed from the known devR sequence would be useful. Thus, in the absence of secondary considerations, the selection of any primer pair from a known gene sequence is *prima facie* obvious.

Also, as noted in *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)), the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397).

In this case, the complete nucleotide sequence of the *Mycobacterium tuberculosis* devR gene was disclosed in the prior art of GenBank Accession No. U22037 and presented the ordinary artisan with a finite number of possible primers for amplification. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well, an ordinary artisan would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the combined teachings of the cited references. The *KSR* decision makes clear that an explicit teaching, suggestion, or motivation is not required to establish a *prima facie* case of obviousness when an ordinary artisan would have combined known elements according to known procedures with predictable results (MPEP 2141). In this case, the complete nucleic acid sequence of the devR gene was known in the art as evidenced by GenBank Accession Number

U22037. Also, methods of primer synthesis and design were known in the art and were predictable as evidenced by the teachings of Chakravorty, Buck, and Marchetti. Thus, an ordinary artisan would have designed the claimed primers using the known devR sequence and known oligonucleotide synthesis methods and would have expected predictable results in doing so. Thus, in the absence of secondary considerations, the claimed primers are *prima facie* obvious over the cited references. Since Applicant's arguments were not found persuasive, the rejection has been maintained.

Conclusion

9. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Angela M Bertagna/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637